Complications of Immobilization and Bed Rest

Part 1: Musculoskeletal and cardiovascular complications

DOUGLAS K. DITTMER, MD, FRCPC
ROBERT TEASELL, MD, FRCPC

SUMMARY

Prolonged bed rest and immobilization inevitably lead to complications. Such complications are much easier to prevent than to treat. Musculoskeletal complications include loss of muscle strength and endurance, contractures and soft tissue changes, disuse osteoporosis, and degenerative joint disease. Cardiovascular complications include an increased heart rate, decreased cardiac reserve, orthostatic hypotension, and venous thromboembolism.

RÉSUMÉ

L'immobilisation et le repos au lit prolongé engendrent inévitablement des complications qui sont beaucoup plus faciles à prévenir qu'à guérir. Parmi les complications musculo-squelettiques, notons la perte de force et d'endurance musculaire, les contractures et les changements tissulaires, l'ostéoporose due à l'inactivité et l'arthropathie dégénérative. Quant aux complications cardiovasculaires, on y retrouve une accélération du rythme cardiaque, une diminution de la réserve cardiaque, l'hypertension orthostatique et la thromboembolie veineuse.

Can Fam Physician 1993;39:1428-1437.

BED REST AND IMMOBILIZATION are time-honoured treatments for managing trauma and acute and chronic illnesses. Although bed rest and immobilization often benefit the acutely affected part of the body, when prolonged, they often harm the rest of the body. Only within the last four decades have clinicians become aware of the harmful effects of bed rest and inactivity and the beneficial effects of activity.[1] Problems arising from immobilization can complicate a primary disease or trauma and might actually become greater problems than the primary disorder.

Complications of immobilization are much easier to prevent than to treat. Many types of immobilizations can lead to complications:

- enforced bed rest (illness or convalescence);
- paralysis;
- immobilizations of body parts with braces, casts, or corsets;
- joint stiffness and pain with protective limitations of motion;
- mental disorders (catatonia, hysterical paralysis); and
- loss of sensation: discomfort does not dictate change of position.

Dr Dittmer *and* **Dr Teasell** *are on staff in the Department of Physical Medicine and Rehabilitation at the University of Western Ontario in London, Ont.*

Chronically ill, disabled, and geriatric people are particularly at risk.[2] These people already have little or no reserve physiologic function, and any additional difficulties created by immobilization result in functional losses. *Table 1* lists musculoskeletal and cardiovascular complications of bed rest and immobilization.

Musculoskeletal complications

Muscle weakness and atrophy. The most obvious effect of prolonged immobilization is loss of muscle strength and endurance. A muscle at complete rest loses 10% to 15% of its strength each week. Nearly half of normal strength is lost within 3 to 5 weeks of immobilization. Patients immobilized in bed and astronauts[3-5] in zero gravity (*Figure 1*) find the first muscles to become weak and atrophic are those of the lower extremities and trunk that normally resist gravity.[1] The antigravity muscles are reported to experience greater loss of strength than other skeletal muscles with inactivity and a greater proportional loss of muscular

torque.[6] Postural and locomotive muscles lose their tension-generating capacity.

Generalized muscle weakness hampers people in the activities of daily living, work, climbing stairs, and even walking. Local muscle weakness results from local immobilization when fractured bones or injured joints are set in casts (*Figure 2*).[7,8] LeBlanc et al[9] demonstrated changes in muscle atrophy and strength after immobilization among nine male volunteers given absolute horizontal bed rest. They used magnetic resonance imaging to calculate muscle area and a Cybex II dynamometer to measure strength. The muscle area of the plantar flexors (gastrocnemius and soleus) decreased 12% and strength decreased 26%; dorsiflexion muscle area and strength were not significantly decreased. These results have implications for patients with severe orthopedic and neurologic disorders and for persons who are voluntarily inactive (many of the elderly).

Unfortunately the rate of recovery from disuse weakness is slower than the rate of loss. Disuse weakness is reversed at a rate of only 6% per week using submaximal exercise (65% to 75% of maximum).[8] Muscle strength can be maintained without loss or gain with daily muscle contractions of 20% or more of maximal tension for several seconds each day.[1] Functional electrical stimulation and biofeedback training can increase or maintain muscular strength in those muscles with less than antigravity strength.

Complete rest will also result in decreased endurance through a reduction in muscle strength, metabolic activity,[10] and circulation. Decreased endurance levels that cause a sense of fatigue and reduce patient motivation set up a vicious circle of greater inactivity and (both as a contributing factor to and a result of) further fatigue.

Muscle atrophy is defined as loss of muscle mass. It might account for a decrease in muscle strength and endurance. Normal muscles at rest can lose half their bulk after only 2 months.[8] During flaccid paralysis (ie, peripheral nerve injury) a totally denervated muscle can lose as much as 95% of its bulk. With irreversible denervation, muscle fibres undergo permanent degeneration and are replaced by fat and connective tissue. In spastic (eg, stroke) paralysis or in patients whose limbs are immobilized by splinting, the degree of muscle atrophy is less, generally around 30% to 40%. Combined muscle atrophy, decreased strength, and limited endurance leads to poor coordination of the movements of the extremities and could affect the patient's ability to perform the activities of daily living.

Contractures and soft tissue changes. Contractures, defined as fixed deformities of joints as a consequence of immobilization, occur because of the dynamic nature of connective tissue and muscle in the body. Connective tissue is constantly being removed, replaced, and reorganized and can be seen to go through a series of phases during healing.[11] In areas of frequent movement, loose areolar connective tissue develops. In areas of little or no motion, collagen eventually is laid down as a dense mesh of sheets. Collagen fibres maintain their length if frequently stretched but shorten if immobilized.

Ligament complexes are affected biomechanically, biochemically, and morphologically by immobilization, and these changes occur in both bony ligament insertions and the ligament substance itself.[12,13] Hence, after trauma to the soft tissue and bone, it is important to realize that immobilization in a cast with non–weight-bearing status (eg, a lower limb fracture) can lead to changes that are difficult to reverse later. Experiments with animals have shown that, after 8 weeks of immobilization in whole body casts, knee ligament stiffness, maximum load at failure, and energy absorption before failure decreased to 69%, 61%, and 68% of normal, respectively, and that the ligaments had not returned to normal even 1 year later.[14,15]

Immobilization can cause fibrofatty infiltration in joints that can mature into strong adhesions within the joints and might destroy cartilage. In periarticular connective tissue, increased cross-linkage between existing collagen and new type I collagen that has been abnormally deposited within the matrix contributes to contracture rather than to the synthesis of a new type of collagen.[16] Shortening collagen fibres can restrict movement significantly even within

Table 1. **Potential complications of immobilization**

MUSCULOSKELETAL
- Decreased muscle strength and atrophy
- Decreased endurance
- Contracture
- Osteoporosis

CARDIOVASCULAR
- Increased heart rate
- Decreased cardiac reserve
- Orthostatic hypotension
- Venous thromboembolism

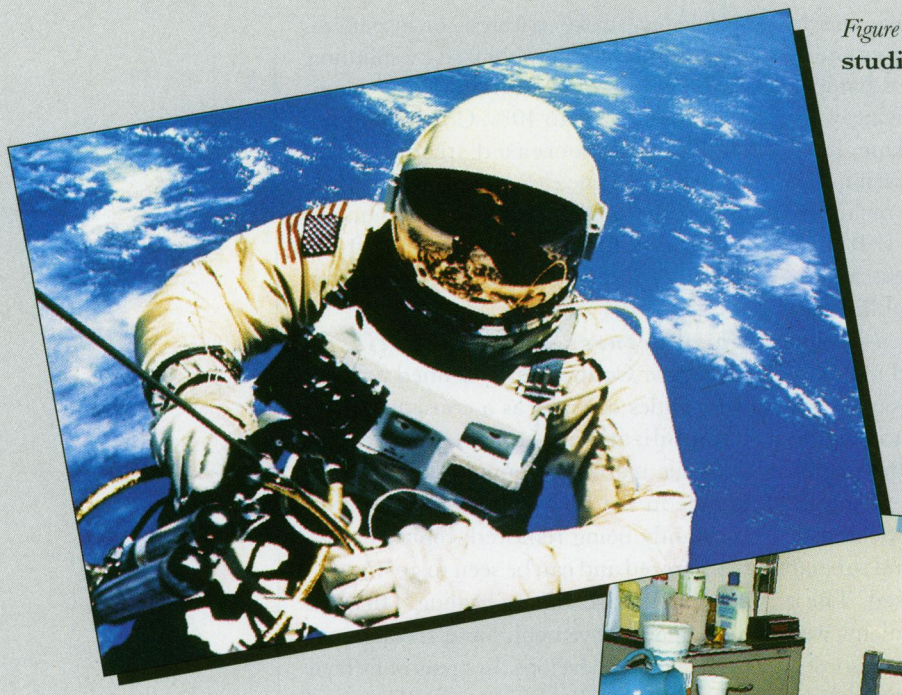

Figure 1. **Early immobilization studies from space research**

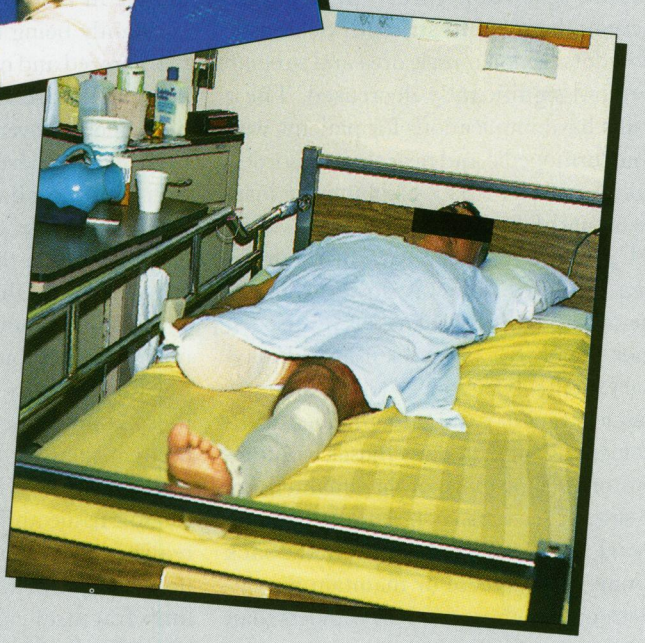

Figure 2. **Patient on bed rest**

1 week. If a joint has to be immobilized, Jarvinen et al[17] suggest that immobilizing the gastrocnemius muscle-tendon unit in a lengthened position causes less muscle atrophy and less decrease in tensile properties than immobilizing in a shortened position.

Many factors contribute to contractures. Denervated muscle (with no opposition to antagonistic muscle) or spasticity (where either flexor or extensor muscle are favoured) can lead to dynamic muscle imbalance. Improper bed positioning can result in deformities, particularly in joints of the lower extremities. Adaptive shortening of soft tissues when the limb is held in a shortened position (eg, in a cast) might occur. Sometimes contractures arise from the disease itself, such as intrinsic muscle changes during a variety of muscle degenerative and inflammatory disorders; soft tissue disorders, such as scleroderma or burns; and joint degenerative or inflammatory disorders. Contractures are most commonly seen in individuals with joint diseases or paralysis of a muscle group or in elderly individuals who are frail, cognitively impaired, or very passive. Muscles that cross two joints, such as the hamstring or back muscles, tensor muscles of fascia lata, rectus muscle of the thigh, gastrocnemius muscles, and biceps muscles, are particularly at risk of shortening during immobilization.[1]

Contractures limit positioning, making bathing and transfers difficult; increase the risk of pressure sores; are often painful; and sometimes prevent ambulation and lengthen hospital stays. For instance, a hip

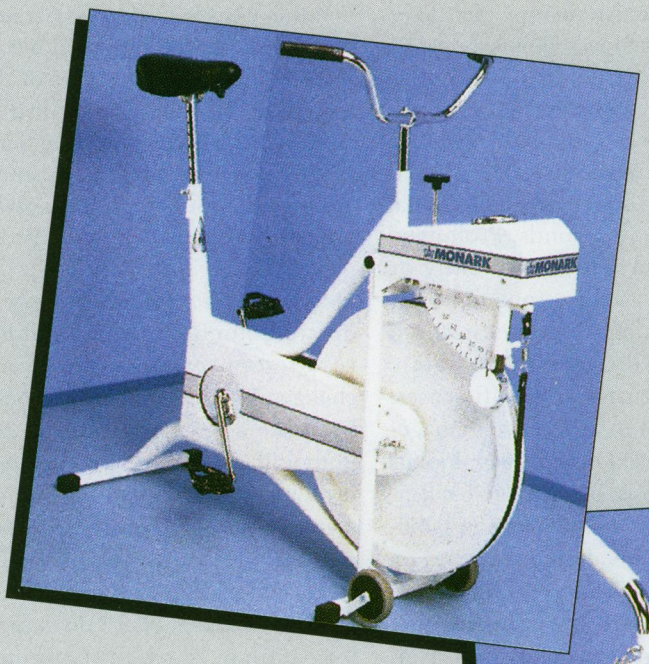

Figure 3. **Bicycle ergometer**

Figure 4. **Arm ergometer**

flexion contracture shortens stride, increases lumbar lordosis, causes the hamstring muscle to shorten resulting in a flexion contracture, and leads to increased energy consumption while moving.[1]

Treatment of contractures emphasizes prevention. Varying the positions of immobile joints regularly, performing active or passive range-of-motion exercises twice daily, and using resting splints for joints that tend to maintain an undesirable position help prevent contractures. Abundant evidence appears to show that early active mobilization after initial stabilization is beneficial. Achilles tendon ruptures and ankle sprains seem to recover with greater strength and sooner (allowing earlier return to work) when early functional activities are permitted than when casts are used.[18,19] Functional braces or hinged casts have also helped to avoid "cast disease." Work by Sarmiento and Latta[20] has shown that, after initial stabilization and formation of early callus, joints associated with the fracture can be mobilized if properly braced to prevent rotation. Eriksson[21] first promoted cast bracing following knee ligament repair to decrease muscle atrophy and obtain a quicker return of motion.

Continuous passive motion has also been used to diminish the effects of immobilization after surgery by enhancing reabsorption of the hemarthrosis; decreasing adhesions, pain, thrombophlebitis, and muscle atrophy; and improving cartilage nutrition, range of motion, and collagen orientation and strength. Yet continuous passive motion alone showed no significant

advantages over active therapy after knee ligament reconstructions.[22] Joints should be immobilized in the neutral position so opposing muscles are at equal length and tension.[23-26]

Established contractures are treated with passive range of motion and terminal stretch for 20 to 30 seconds. Prolonged stretch can be provided manually or through traction devices applied at low tension after heating the tissues involved to 40° to 45°C. Progressive dynamic splinting can be used in specific cases. Contraindications to aggressive management of immobilized or contracted joints include osteoporosis, heterotopic ossification, acute arthritis, ligamentous instability, new fractures, insensate areas, and an inability to communicate pain. If contractures are significantly impeding function and do not respond to conservative management, surgery might be required. After contractures are overcome, the factors that caused them will remain and a preventive maintenance program is a necessity.

Disuse osteoporosis. Like connective tissue, bone is a dynamic tissue. A constant equilibrium is maintained between bone formation and resorption. Bone morphology and density depend on forces that act upon the bone,[27,28] such as the direct pulling action of tendons and weight bearing. Astronauts in weightless environments suffer profound loss of bone mass despite rigorous physical activity. Immobilization leads to bone mass loss in association with hypercalciuria and negative calcium balance.[29] Loss is generally greater with lower motor neuron flaccid lesions than with upper motor neuron spastic lesions.

Experimental studies demonstrate that increased bone resorption accounts for loss of bone mass[28,30-33] even though the parathyroid hormone is not suppressed. Both cortical and trabecular bone are lost, trabecular bone predominantly.[34] Trabecular bone is found in the spine, femur, and wrist, making these areas susceptible to fractures after trauma. Bone loss during long-term immobilization tends to occur in stages: first, rapid bone loss; second, beginning at 12 weeks, slower but more prolonged bone loss; until third, stabilization at 40% to 70% of original mass.

Osteoporosis can lead to fractures of the spinal vertebrae, femur, and distal radius. Repeated anterior fractures of the spinal vertebrae result in a dorsal kyphosis and chronic back pain. But osteopenia sometimes is undetected for years. Routine radiographs do not demonstrate osteoporosis until 40% of bone density is lost.

Degenerative joint disease. Experimental immobilization of animals has resulted in severe degenerative joint changes.[30,35] Researchers now believe that both the contracted capsule and joint immobilization in a fixed position cause prolonged compression of the cartilage contact sites and their subsequent degeneration.[1] These findings have not been correlated with human subjects. The earlier work of Salter et al[36] on damaged rabbit cartilage showed that continuous passive motion had a beneficial biologic effect on the healing of full thickness defects in articular cartilage.

Finally, one randomized, clinical trial of bed rest treatment for mechanical low back pain without neuromotor deficits showed convincingly that the sooner patients were up and moving around (ie, after 2 days' rest rather than 7 days') the fewer days of work they missed. No differences in other functional, physiologic, or perceived outcomes were noted.[37] Bed rest to allow an underlying lesion to heal by avoiding biomechanical strain clearly is being challenged as a useful way to treat musculoskeletal injury.

Cardiovascular complications

Cardiovascular complications of immobilization include an increased heart rate, decreased cardiac reserve, orthostatic hypotension, and venous thromboembolism.

Increased heart rate and decreased cardiac reserve. Heart rate increases (generally to more than 80 beats/min) following immobilization, probably due to increased sympathetic nervous system activity. During bed rest, the resting pulse rate speeds up one beat each minute every 2 days.[38] Because the increased heart rate results in less diastolic filling time and a shortened systolic ejection time, the heart is less capable of responding to metabolic demands above the basal level. Shorter

diastolic time reduces coronary blood flow and decreases the oxygen available to cardiac muscle. Cardiac output, stroke volume, and left ventricular function decline overall.[38-41] Physical exertion can then lead to tachycardia and angina in predisposed individuals and work capacity is reduced. In a classic study by Saltin et al,[42] 24 male college students were subjected to 20 days of bed rest. Results showed a 27% decrease in maximal O_2 uptake, 25% decrease in stroke volume, 15% to 26% increase in cardiac output, and a 20% increase in heart rate.

To reverse the effects of bed rest and build endurance, patients should exercise to between 50% and 70% of maximal oxygen consumption, or 65% to 75% of maximal heart rate. Maximal heart rate (beats/min) can be calculated as 210 - (age in years · 0.65). This formula is justified when, apart from deconditioning, the patient has no evident heart disease. Target heart rates can be achieved using treadmill or bicycle ergometer (*Figure 3*) training, or arm ergometry (*Figure 4*) for patients with lower limb injury or disease.

Orthostatic hypotension. Orthostatic hypotension is believed to occur when the cardiovascular system does not adapt normally to an upright posture. It occurs after 3 weeks of bed rest (earlier for the elderly) because of excessive pooling of blood in the lower extremities and a decrease in circulating blood volume. This, along with a rapid heart rate, results in diminished diastolic ventricular filling and a decline in cerebral perfusion.[39,43] The circulatory system is unable to restore a stable pulse and blood pressure level. Generally, orthostatic hypotension is characterized by a pulse rate increase of more than 20 beats/min and a 70% or more decrease in pulse pressure with venous pooling in the legs.

Treatment of orthostatic hypotension involves leg exercises, early mobilization and ambulation, and elastic stockings. In cases of prolonged bed rest, a tilt table with graduated increase in the standing posture might be necessary. Reconditioning the cardiovascular system generally takes longer than deconditioning. Reconditioning appears to take even longer for elderly patients.

Venous thromboembolism. Venous thromboembolism is due primarily to venous stasis and to a lesser degree to increased blood coagulability (two of the three factors in Virchow's triad). Stasis occurs in the legs following decreased contraction of the gastrocnemius and soleus muscles. Most deep venous thrombi occur in the calf and mainly originate in the soleus sinus. Researchers believe that 80% of the clots lyse before reaching the level of the knee. Patients with proven deep venous thrombi involving the popliteal or more proximal leg veins have a 50% chance of developing pulmonary emboli.[44] Mortality from untreated pulmonary embolism is 20% to 35%.[45] Organization and resolution of a deep venous thrombosis occurs within 7 to 10 days. Length of bed rest is directly related to frequency of deep venous thrombosis.[46]

Most patients who develop deep venous thrombosis fail to demonstrate any clinical signs. Venous collaterals are generally so well developed that the thrombi must be quite extensive to clog the veins or cause vessel wall inflammation. Clinical signs of deep venous thrombosis tend to be unreliable. These include pain and tenderness, swelling, venous distention, pallor, cyanosis, redness, or a positive Homans' sign. More than 50% of patients who have clinical signs of deep venous thrombosis have no evidence of it on venography.[47] Clinical diagnosis is both nonsensitive and nonspecific, and it is important to verify clinical suspicions with diagnostic tests such as Doppler ultrasonography, impedance plethysmography, and contrast venography. Each test has specific advantages and disadvantages; contrast venography is the gold standard.

The clinical picture of pulmonary thromboembolism is both nonspecific and poorly sensitive. Symptoms of pulmonary emboli include dyspnea, tachypnea, tachycardia, pleuritic chest pain, cough, hemoptysis, or a pleural rub or effusion.[48] Less specific signs include fever, confusion, wheezing, and arrhythmia. Severe cases might lead to pulmonary consolidation or atelectasis, right heart failure, and even cardiovascular collapse with hypotension. The key diagnostic test is a lung scan for ventilation and perfusion. Generally, a

mismatch is present with parts of the lung appearing adequately ventilated but not adequately perfused. Arterial blood gases could show a fall in the arterial oxygen level and no change in the arterial carbon dioxide level. An electrocardiogram can rule out myocardial infarction.

Treating venous thromboembolism involves decreasing venous stasis by such physiotherapy as leg exercises, leg elevation, elastic stockings, early ambulation, and mechanical compression. Methods to decrease blood coagulability include dextran, antiplatelet drugs such as acetylsalicylic acid, and anticoagulants such as warfarin and heparin. Prophylactic methods that effectively prevent venous thromboembolism include low-dose heparin, intermittent pneumatic compression, oral anticoagulants, and dextran. Heparin has significantly decreased deep venous thrombosis in many trials and is required only in low doses because it does not amplify the coagulation cascade seen with established venous thrombi. Treatment should continue until the patient is ambulatory. ■

Requests for reprints to: *Dr Douglas K. Dittmer, Victoria Hospital, 800 Commissioners Rd E, London, ON N6A 4G5*

References

1. Halar EM, Bell K. Rehabilitations' relationship to inactivity. In: Kottke FJ, Lehmann JF, editors. *Krusen's handbook of physical medicine and rehabilitation.* 4th ed. Philadelphia: WB Saunders Co, 1990:1113-39.
2. Bonner CD. Rehabilitation instead of bedrest? *Geriatrics* 1969;24:109-18.
3. Herbison GJ, Talbot JM. Muscle atrophy during space flight: research needs and opportunities. *Physiologist* 1985;28:520-4.
4. Riley DA, Ellis S. Research on the adaptation of skeletal muscle to hypogravity: past and future directions. *Adv Space Res* 1983;3(9):191-7.
5. Thorton WE, Rummel JA. Muscular deconditioning and its prevention in spaceflight. Proceedings of the Skylab Life Sciences Symposium. *J Am Space Agency TMX* 1974;58154:403-16.
6. Gogia PP, Schneider VS, LeBlanc AD, Krebs J, Kasson C, Pientok C. Bedrest effect on extremity muscle torque in healthy men. *Arch Phys Med Rehabil* 1988;69:1030-2.
7. MacDougall JD, Elder GCB, Sale DG, Moroz JR, Sutton JR. Effects of strength training and immobilization of human muscle fibres. *Eur J Appl Physiol* 1980;43:25-34.
8. Muller EA. Influence of training and of inactivity on muscle strength. *Arch Phys Med Rehabil* 1970; 51:449-62.
9. LeBlanc A, Gogia P, Schneider V, Krebs J, Schonfeld E, Evans H. Calf muscle area and strength changes after five weeks of horizontal bed rest. *Am J Sports Med* 1988;16:6,624-9.
10. MacDougall JD, Ward GR, Sale DG, Sutton JR. Biochemical adaptation of human skeletal muscle to heavy resistance training and immobilization. *J Appl Physiol* 1977;43:700-3.
11. Van der Meulen JCH. Present state of knowledge on processes of healing in collagen structures. *Int J Sports Med* 1982;3:4-8.
12. Akeson WH, Amiel D, Abel MF, Garfin SR, Woo SLY. Effects of immobilization on joints. *Clin Orthop* 1987;219:28-37.
13. Walsh S, Frank C, Hart D. Immobilization alters cell metabolism in an immature ligament. *Clin Orthop* 1992;277:277-88.
14. Noyes FR, Torvik PJ, Hyde WB. Biomechanics of ligament failure. II. An analysis of immobilization, exercise and reconditioning effects in primates. *J Bone Joint Surg* Am 1974; 56A:1406-18.
15. Zarins B. Soft tissue injury and repair – biomechanical aspects. *Int J Sports Med* 1982;3:9-11.
16. Amiel D, Akeson WH, Harwood FL, Mechanic GL. The effect of immobilization on the types of collagen synthesized in periarticular connective tissue. *Connect Tissue Res* 1980;8:27-32.
17. Jarvinen MJ, Einola SA, Virtanen EO. Effect of the position of immobilization upon the tensile properties of the rat gastrocnemius muscle. *Arch Phys Med Rehabil* 1992;73:253-7.
18. Brooks SC, Potter BT, Rainey JB. Treatment for partial tears of the lateral ligament of the ankle: a prospective trial. *BMJ* 1981;282:606-7.
19. Enwemeka CS, Spielholz NI, Nelson AJ. The effect of early functional activities on experimentally tenotomized Achilles tendons in rats. *Am J Phys Med Rehabil* 1988;67(6):264-9.
20. Sarmiento A, Latta LL. *Closed functional treatment of fractures.* New York: Springer-Verlag, 1981.
21. Eriksson E. Sports injuries of the knee ligaments: their diagnosis, treatment, rehabilitation, and presentation. *Med Sci Sports Exerc* 1976;8:133-44.
22. Rosen MA, Jackson DW, Atwell EA. The efficacy of continuous passive motion in the rehabilitation of anterior cruciate ligament reconstructions. *Am J Sports Med* 1992;20:122-7.

23. Spector SA, Simard CP, Fournier M, Sternlicht E, Edgerton VR. Architectural alterations of rat hind-limb skeletal muscle immobilized at different lengths. *Exp Neurol* 1982;76:94-110.
24. Spence WA, Vallbona C, Carter RE. Physiologic concepts of immobilization. *Arch Phys Med Rehabil* 1965;46:89-100.
25. Stolov WC, Fry LR, Riddel WM, Weilepp TG Jr. Adhesive forces between muscle fibres and connective tissue in normal and denervated rat skeletal muscle. *Arch Phys Med Rehabil* 1973; 54:208-13.
26. Stremel RW, Convertino VA, Greenleaf JE, Bernauer EM. Response to maximal exercise after bedrest [abstract]. *Fed Proc* 1974;33:327.
27. Ede MC, Burr RG. Circadian rhythm of urinary calcium excretion during immobilization. *Aerosp Med* 1973;44:495-8.
28. Uhthoff HK, Jaworski ZFG. Bone loss in response to long-term immobilization. *J Bone Joint Surg* Br 1978;60B:420-9.
29. Issekutz B, Blizzard JJ, Birkhead NC, Rodahl M. Effect of prolonged bedrest on urinary calcium output. *J Appl Physiol* 1966;21:1013-20.
30. Enneking WF, Horowitz M. The intraarticular effects of immobilization on the human knee. *J Bone Joint Surg Am* 1972;54A: 973-83.
31. Heaney RP. Radiocalcium metabolism in disuse osteoporosis in man. *Am J Med* 1962;33:188-200.
32. Landry M, Fleisch H. The influence of immobilization on bone formation as evaluated by osseous incorporation of tetracyclines. *J Bone Joint Surg* Br 1964;46B:764-71.
33. Young DR, Niklowitz WJ, Brown RJ, Jee WS. Immobilization-associated osteoporosis in primates. *Bone* 1986;7:109-17.
34. Carr CE, Genant HK, Young DR. Comparison of vertebral and peripheral mineral losses in disuse osteoporosis in monkeys. *Radiology* 1980;134:525-9.
35. Finsterbush A, Friedman B. Early changes in immobilized rabbit's knee joint: a light and electron microscopic study. *Clin Orthop* 1973;92:305-19.
36. Salter RB, Simmonds DF, Malcolm BW. The biological effect of continuous motion on the healing of full thickness defects in articular cartilage. *J Bone Joint Surg* Am 1980;62A:1232-51.
37. Deyo RA, Diehl AK, Rosenthal M. How many days of bed rest for acute low back pain? *N Engl J Med* 1986;315:1064-70.
38. Halar EM, Bell KR. Contracture and other deleterious effects of immobility. In: DeLisa JA, editor. *Rehabilitation medicine, principle and practices.* Philadelphia: JB Lippincott, 1988:448-62.
39. Holmgren A, Mossfeldt F, Sjostrand T, Strom G. Effect of training on work capacity, total hemoglobin, blood volume, heart volume and pulse rate in recumbent and upright positions. *Acta Physiol Scand* 1960;50:73-83.
40. Taylor HL, Henschel A, Prozek J, Keys A. Effects of bedrest on cardiovascular function and work performance. *J Appl Psychol* 1949;2:223-9.
41. Taylor HL. The effects of rest in bed and of exercise on cardiovascular function. *Circulation* 1968;38:1016-7.
42. Saltin B, Blomqvist G, Mitchell JH, Johnson RL, Wildenthal K, Chapman CB. Response to exercise after bed rest and after training – a longitudinal study of adaptive changes in oxygen transport and body composition. *Circulation* 1968;38(Suppl 7):1-78.
43. Chobanian AV, Lillie RD, Tercyak A, Blevins P. The metabolic and hemodynamic effects of prolonged bedrest in normal subjects. *Circulation* 1974;49:551-9.
44. Hirsh J, Hull R. Natural history and clinical features of venous thrombosis. In: Colman RW, Hirsh J, Marder VJ, Salzman EW, editors. *Hemostasis and thrombosis: basic principles and clinical practice.* Philadelphia: JB Lippincott, 1982:831-43.
45. Tibbutt DA, Chesterman CN. Pulmonary embolism: current therapeutic concepts. *Drugs* 1976;11:161-92.
46. Micheli LJ. Thromboembolic complications of cast immobilization for injuries of the lower extremities. *Clin Orthop* 1975;108:191-5.
47. Hull R, Hirsh J, Sackett DL. Cost effectiveness of clinical diagnosis, venography, and non-invasive testing in patients with symptomatic deep vein thrombosis. *N Engl J Med* 1981;304:1561-7.
48. Bell WR, Simon TL, Demets DL. The clinical features of submassive and massive pulmonary emboli. *Am J Med* 1977;62:355-60.

• • •